

Investigation of possible aqueous phase formation during vaporization of sevoflurane

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Abstract

Background and Aims: Ultane[®] (sevoflurane; AbbVie Inc., North Chicago, IL, USA) has a dissolved water content of approximately 0.035% weight/weight (w/w). A previous report described formation of an aqueous layer in 4 of 13 sevoflurane vaporizers used in operating rooms. We investigated the conditions under which an aqueous layer could develop during vaporization of sevoflurane–water mixtures.

Material and Methods: A temperature-controlled glass reactor was used to simulate a vaporizer. In four experiments, the vaporization of different sevoflurane–water mixtures was monitored over approximately 3–4 days. Samples were removed at regular intervals for analysis of water content. For confirmation, one experiment was replicated in a Tec 7 vaporizer.

Results: Saturation of sevoflurane with water occurred at 0.11%–0.13% w/w at an ambient temperature; at greater water concentrations a separate aqueous phase was initially present. The sevoflurane–water azeotrope contained approximately 1.2% w/w water at 25°C. When the initial water content was <1.2% w/w (0.11%–1.03% w/w), vaporization resulted in a single phase of drier sevoflurane (final water concentration 0.02%–0.08% w/w). When the starting water concentration exceeded the azeotropic concentration (5.0% w/w), vaporization increased the water content, reaching 13% w/w at 71 h. Results under the low initial water condition were similar in the Tec 7 vaporizer.

Conclusions: An increase in water concentration following vaporization of sevoflurane can only occur when the starting water content is higher than the azeotropic concentration and therefore cannot originate from the dissolved water present in the marketed product because the water concentration in Ultane[®] is 34 times lower than the azeotropic concentration.

Keywords: Anesthesia, sevoflurane, water

Introduction

A 2016 case report described the formation of an aqueous layer, which was found to be positive for *Staphylococcus epidermidis*, within 4 of 13 hospital vaporizers containing sevoflurane (Ultane[®]; AbbVie Inc., North Chicago, IL, USA).^[1] Examination of unopened sevoflurane bottles did not reveal an aqueous layer,^[1] and a check of the

original batch and manufacturing lot by AbbVie revealed no abnormalities (AbbVie data on file). The origin of this aqueous layer in the vaporizers was unknown, and it was hypothesized that the low amount of water in the commercial product preferentially accumulated in the vaporizer, leading to the formation of the aqueous phase.

Dissolved water is present at controlled levels in sevoflurane to inhibit its degradation, catalyzed by Lewis acids such as metal oxides and metal halides, to hydrofluoric acid and other toxic compounds.^[2] Of marketed sevoflurane products, Ultane[®] has the highest water content [approximately 350 ppm, which

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is equivalent to 0.035% weight for weight (w/w)].^[2] This water content is well below the azeotropic concentration of a sevoflurane–water mixture.

An azeotrope produces a vapor of exactly the same composition as the liquid being vaporized. The liquid being vaporized does not change in composition as the vaporization of an azeotrope proceeds. A minimum boiling azeotrope is present when the boiling point of the mixture is lower than the boiling point of the pure components and is an anomaly caused by the large molecular dissimilarity between the components. The sevoflurane–water system is noted to form a minimum boiling azeotrope, and because the two components have limited miscibility, the azeotrope splits into a sevoflurane phase (saturated with water) and an aqueous phase (saturated with sevoflurane).^[3] The boiling point of sevoflurane is 58.5°C at 1 atmosphere (atm).^[4] As it is characteristic of all azeotropic systems, although counterintuitive, it is true that in a two-component minimum boiling azeotropic system such as sevoflurane–water, where water is the higher boiling component (100°C at 1 atm), water is expected to vaporize preferentially with respect to sevoflurane at mixture compositions below the azeotropic concentration of water in sevoflurane–water. Hence, preferential vaporization of water is also expected when water is present below the saturation solubility of water in sevoflurane. However, there is no published information on the azeotrope composition for sevoflurane–water; the azeotrope composition around 25°C is relevant for the vaporization case being discussed here.

Because the water concentration in Ultane® (0.035% w/w) is significantly lower than the solubility limit (about 0.12% w/w water), the water remains dissolved. For vaporization of mixtures with water content lower than the solubility limit (0.12%), water is expected to vaporize preferentially, and hence, separation of water as an aqueous layer is not expected. This can be demonstrated by the vaporization of sevoflurane–water mixtures and is essential for understanding its behavior in vaporizers.

To improve the understanding of the vaporization of azeotropic compositions of sevoflurane and water, a comprehensive study was designed and conducted. The objective of this study was to determine whether an aqueous layer can form from the dissolved water content in sevoflurane during vaporization with medical-grade dry air. For a more complete understanding, the vaporization of sevoflurane–water was studied at the azeotropic composition, as well as above and below that point. We tested the hypothesis from the previous case report that vaporization of marketed sevoflurane (Ultane®) could lead to a selective accumulation of water, potentially forming an aqueous layer.

Material and Methods

Materials

SevoFlo® (Abbott Laboratories, North Chicago, IL, USA) for animal use, which is manufactured in the same line and has the same composition as Ultane®,^[5,6] was used as the sevoflurane source for all experiments because it was more readily available. Both products have the same miscible water content of approximately 0.035% w/w. Other experimental materials included deionized water and dry air (Ultra Zero Air, Praxair, Danbury, CT, USA).

Procedure

The ability of sevoflurane to form a minimum azeotrope was tested by the characteristic boiling point depression of a mixture of sevoflurane and water. To explore the phase behavior, various mixtures of sevoflurane and water were vaporized in four experiments, each using approximately 2 L of sevoflurane–water. For the experiments requiring sevoflurane saturated with water, the two components were mixed vigorously to ensure saturation. The water-saturated sevoflurane layer was separated by settling and transferred into a clean, dry glass reactor with a jacket equipped with an agitator and glass frit air bubbler. To create a second phase for some of the experiments, additional water was added beyond saturation. The glass reactor setup facilitated visualization of the contents while mimicking the vaporization in a Tec 7 vaporizer (General Electric Healthcare, Waukesha, WI, USA). The glass reactor was kept at a constant temperature of 25°C ± 1°C by circulating glycol–water through the jacket using a thermostatic circulator (Julabo, Seelbach, Germany). The air flow rate through the frit was kept at 130 mL/min (25°C and 1 atm). An upper limit on the vaporization time was imposed by the level of liquid in the reactor falling below the frit of the air bubbler and occurred at a volume of approximately 0.6–0.7 L; run 1 lasted approximately 2 days, whereas runs 2–4 lasted approximately 3 days each. In run 1, single-phase sevoflurane–water (containing measured 0.11% total water w/w) was used and vaporized with agitation at 300 rpm. For subsequent runs, more vigorous agitation (450 rpm) was used to keep the sevoflurane and aqueous phases well mixed, except for stopping agitation when draining the reactor for phase measurements. For run 2, 0.4% w/w water was added to the water-saturated sevoflurane (total water content about 0.5% w/w), forming a separate aqueous layer that was dispersed by the agitation during vaporization. For run 3, additional water (0.9% w/w water) was added to sevoflurane saturated with water to reach about 1.03% w/w total water content at the start of vaporization. For run 4, additional water was added to

sevoflurane to reach about 5.0% w/w total water content before starting vaporization. The weights of the sevoflurane and aqueous phases in runs 3 and 4 were measured at various times during the vaporization by draining the liquid from the glass reactor after briefly stopping the agitation, separating the phases, weighing the phases, adding them back, and continuing the vaporization.

To confirm the results obtained in the glass reactor that simulated the vaporization in a Tec 7, an experiment (run 5) similar to run 1 was conducted in a Tec 7 vaporizer mounted in a portable anesthesia machine (General Anesthetic Services, South Park, PA, USA). After conditioning with dry air, the vaporizer was filled with water-saturated sevoflurane (0.12% w/w water). Approximately 2 h were allowed to elapse for saturating the wick with sevoflurane, after which additional water-saturated sevoflurane was added to fill the reservoir to its maximum recommended volume (total liquid added was 270 mL). The vaporization was conducted at 20°C (instead of 25°C used for vaporization in the glass reactor) with dry air at a flow rate of 3 L/min and a setting of 2% anesthesia to mimic the cooler conditions in most operating rooms. Vaporization was followed for 6.5 h; when the liquid level had reached the low mark in the sight glass, the remaining liquid was drained and tested to determine its water content.

Analysis

The concentration of water in sevoflurane was measured using a validated Karl Fischer method according to the USP 39 General Chapter <921> Method 1 by titration. Weights were measured with an analytical balance (Mettler, Columbus, OH, USA, or Sartorius, Göttingen, Germany).

Results

The boiling point of sevoflurane alone was determined to be 58.9°C at a pressure of 0.996 atm, in close agreement with the literature value of 58.5°C at 1 atm.^[4] Addition of water to 0.5% w/w depressed the boiling point of the mixture to

56.1°C, indicating that a minimum boiling azeotrope was formed.

Results of the vaporization experiments in the glass reactor are shown in Table 1 and schematically in Figure 1. When sevoflurane saturated with water was used for the vaporization (run 1; initial water content, 0.11% w/w), the concentration of water declined sharply by Day 1 and continued to decrease by Day 2, after which time the experiment was halted (last measured water content, 0.02% w/w). When a small amount of water was added to water-saturated sevoflurane (run 2; extra 0.4% w/w; total starting water concentration in reactor, approximately 0.50% w/w), a separate aqueous layer was observed initially (reactor contents were turbid) but disappeared between Days 2 and 3 (reactor contents were clear), at which time the remaining sevoflurane layer became drier (last measured water content, 0.04% w/w). When a greater quantity of water was added to water-saturated sevoflurane (run 3; extra 0.9% w/w added to water-saturated sevoflurane with 0.13% w/w water; total starting water concentration approximately 1.03% w/w), the aqueous phase persisted over the 3-day time frame of the experiment, and the liquid in the reactor remained turbid throughout the run. However, the water phase ratio of 0.9% w/w, reported as the ratio of the aqueous phase weight to the sevoflurane phase

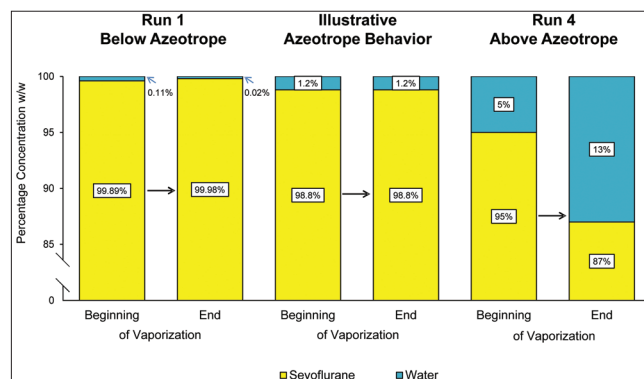


Figure 1: Relative concentrations (w/w) of sevoflurane and water at the beginning and end of vaporization at 25°C in two experiments in relationship to their azeotropic behavior. w/w = weight for weight

Table 1: Initial and final conditions of sevoflurane-water vaporization experiments

Run	Concentration of water, % w/w			Duration of vaporization, h	Initial condition relative to azeotrope	Final state of sevoflurane layer
	Initial in sevoflurane layer	Initial in reactor	Final			
Glass reactor						
1	0.11	0.11	0.02*	44	Below	Drier
2	0.11	0.50	0.04*	73	Below	Drier
3	0.13	1.03	0.13*, 0.8 [†]	66	Near	Little change
4	ND	5	13 [†]	71	Above	Wetter
Tec 7 vaporizer						
5	0.12	0.12	0.03*	6.5	Below	Drier

ND=Not determined; w/w=Weight for weight. *Concentration in sevoflurane layer. [†]Concentration in reactor

weight in percent at the start, decreased slowly and steadily to 0.8% after 2.75 days of vaporization.

When a much larger quantity of water was added to sevoflurane above the azeotropic point (run 4; 5.0% w/w water based on the water added to sevoflurane; Table 1), the aqueous and sevoflurane phases both persisted during the entire vaporization experiment, and the liquid in the reactor was turbid. During this experiment the water phase ratio initially at 5% w/w steadily increased to 13% w/w water phase ratio after 3 days of vaporization. Run 4 is shown as the third case in Figure 1. In this experiment, the vaporized liquid has the composition of the azeotrope, and it may be calculated by determining the amount of water and sevoflurane phases lost from the start of the experiment. After the third day of vaporization, the amount of water phase lost was 23.8 g, the amount of sevoflurane phase lost was 2017.8 g, and, consequently, the azeotrope composition was 1.2% w/w water in sevoflurane.

The experiment in the Tec 7 vaporizer (run 5) used a starting composition similar to run 1 in a glass reactor. The vaporizer was charged with 270 mL sevoflurane saturated with water. The level in the vaporizer was at the maximum mark at the start of the vaporization. At the end of vaporization, when the minimum mark was reached in the Tec 7 vaporizer, the residual liquid was a single phase with a volume of 60 mL. The water content dropped from 0.12% w/w at the start to 0.03% w/w at the end [Table 1], whereas the ending water content was 0.02% w/w in the comparable experiment in the glass vessel (run 1). By material balance (based on volume), the liquid remaining in the wick of the Tec 7 vaporizer was 75 mL, which is in line with the estimate provided in the Tec 7 user manual.

Discussion

The results of this investigation showed that when the starting concentration of water (whether it is above or below its miscibility) is *lower than* the azeotropic concentration of approximately 1.2% w/w, vaporization of sevoflurane–water mixtures proceeds with loss of the water, preventing the preferential accumulation of water in the mixture. There is a preferential loss of water, leading toward a drier state. When the starting concentration of water is at the azeotropic concentration, vaporization maintains the relative amount of aqueous phase to the sevoflurane phase at an invariant level (approximately 1.2% w/w). Because the water content of Ultane[®] at around 350 ppm (0.035% w/w) is 34 times less than the azeotropic concentration, the accumulation of water during vaporization leading to an aqueous phase is not physically possible.

At the azeotropic concentration, sevoflurane and water vaporize with a constant ratio, so that there is no change in the composition of the liquid mixture over time [Figure 2, Example 1]. When two phases are present at the start of the vaporization, with water content lower than the azeotrope, the aqueous layer decreases over time and eventually disappears, after which the content of water dissolved in the remaining sevoflurane continues to decrease due to preferential vaporization of water as the vaporization proceeds [Figure 2, Example 2]. When the water content is higher than the azeotropic concentration, the sevoflurane layer decreases over time and eventually disappears, leaving water saturated with sevoflurane. Vaporization of the sevoflurane leads to higher concentrations of water in this condition [Figure 2, Example 3].

These observations made with sevoflurane–water containing two phases and also a single sevoflurane phase are consistent with those expected from a minimum boiling azeotropic system. To exclude the possibility that there was something different about vaporization in the temperature-controlled glass reactor with agitation, the experiment was also conducted in a Tec 7 vaporizer using clinical conditions, and similar results were found. The experiments with the glass reactor and Tec 7 vaporizer demonstrate that, even when intentionally adding water in sufficient quantities to form a separate layer, as long as the starting water content is less than the azeotrope of about 1.2% w/w, vaporization leads to preferential disappearance of the aqueous phase and eventual formation of sevoflurane that is nearly devoid of water.

The introduction of water to sevoflurane to an extent that is equal to or exceeds the azeotropic concentration (1.2% w/w) results in a persistent aqueous layer. The volume of added water necessary to produce a persistent water layer in a Tec 7 vaporizer fully charged with Ultane[®] (approximately 300 mL or 450 g) is calculated to be approximately 5.5 mL. If small amounts of water are inadvertently added to the vaporizer, subsequent refilling of the vaporizer reservoir with fresh Ultane[®] (containing 0.035% w/w water) will dilute the mixture, and eventually any aqueous layer will be depleted. Finally, even when a water layer is present, the vaporized liquid will have the composition of the azeotrope (about 98.8% w/w sevoflurane and 1.2% w/w water), so that the dose of anesthetic delivered to the patient is only slightly lower than expected and may not represent a clinically relevant difference.

The experiments performed in the study were meant to test the phase behavior of a mixture of sevoflurane and water and establish the boundary conditions that could lead to a persistent aqueous phase. The source of the aqueous layer in sevoflurane observed in the previous report^[1] remains

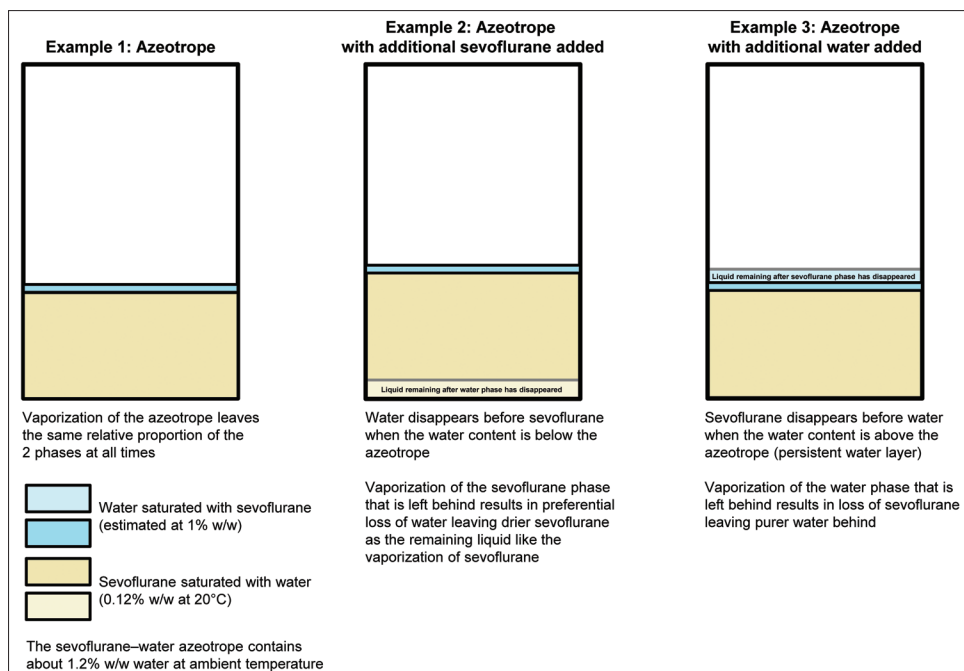


Figure 2: Expected vaporization behavior of sevoflurane--water with two phases present at the start. w/w = weight for weight

uncertain but, based on the results of this investigation, the initial hypothesis of preferential water accumulation from the low starting amount in commercial Ultane[®] causing formation of the aqueous layer needs to be reconsidered.

Water should never be added to vaporization equipment, and the continued dryness of the apparatus should be ensured, for example, at the end of maintenance procedures. A regular visual check for the presence of an aqueous phase by examining the liquid drained from the vaporizer should be considered. The user manual for the Tec 7 vaporizer suggests draining the contents every 2 weeks.

In conclusion, it is not possible to form an aqueous layer as a second phase when sevoflurane is vaporized using dry gas under the ambient conditions that are present in operating rooms. As the source of the water in the previously reported finding remains unknown, routine vaporizer use and maintenance protocols are advised.

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of the data and in the writing, review, and approval of the publication.

Conflicts of interest

Shane Varughese, Vikram G. Kalthod, James P. Petzel, and H. Peter Bacher are employees of AbbVie and may hold AbbVie stock and/or stock options. Arthur W. Wallace has no financial, consulting, or employment relationship with AbbVie. Dr Wallace does not hold stock, stock options, or grants or receive funding of any type from AbbVie. Dr Wallace is employed by the University of California, San Francisco and the San Francisco Veterans Affairs Medical Center.

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